REMARKS

Claims 1 to 9 are pending in this application. Claim 6 has been amended to recite that the claimed polypeptide consists of, in addition to a first amino acid sequence, one or more amino acid sequences that are not identical to any part of a hepatitis B virus envelope protein. Support for this amendment can be found throughout the specification, e.g., at page 1, line 20 to page 2, line 12, page 8, lines 23 to 27, and in claim 6 as originally filed. The amendment adds no new matter to the present application.

Rejection under 35 U.S.C. § 103

Claims 1 to 5 were rejected as allegedly obvious over Khudyakov et al. (J. Virol. 68:7067-7074 (1994)) in view of Chassot et al. (Virology 200:72-78 (1994)) and Yuasa et al. (Virology 181:14-21 (1991)). Applicants respectfully traverse this rejection. The polypeptides recited in claims 1 to 5 differ in length from the polypeptides described in secondary references Chassot and Yuasa and are not made obvious when these references are combined with Khudyakov, the primary reference.

Khudyakov describes construction of a polypeptide that includes a mosaic of antigenic epitopes from two strains of hepatitis E virus (HEV). Khudyakov's stated motivation for constructing such a polypeptide was to prepare synthetic polypeptides suitable for diagnostics (see Khudyakov at page 7072, column 1, second paragraph). Kyudyakov does not teach, for example, a polypeptide that consists of a first amino acid sequence identical to amino acids 1 to 104 of a pre-S protein or a fragment thereof that includes at least amino acids 80-102, and one or more sequences not identical to any part of the pre-S sequence. Khudyakov does not suggest that such a polypeptide should be made. The Office Action at page 3, lines 9 to 11 confirms that Kyudyakov fails to provide this information. Additionally, applicants point out that Kyudyakov fails to teach or suggest the specific sequences recited in dependant claims 2 to 5, e.g., polypeptides wherein the first amino acid sequence is 1-104, 25-104, 42-102, 1-102, 25-102,

59-102, 80-102, 80-104 or 59-104 of SEQ ID NO:34, and polypeptides that include the amino acid sequence of a glutathione S-transferase.

The Office Action also cites Yuasa, which fails to provide the information missing in Khudyakov, the primary reference. Yuasa performed experiments in which peptide mapping was performed on pre-S epitopes capable of inducing neutralizing and non-neutralizing antibodies (see Yuasa at page 15, column 1). To that end, Yuasa constructed a parent plasmid that expressed duck hepatitis virus (DHBV) pre-S and S genes in *Escherichia coli* and a series of deletion mutants of that plasmid (see Fig. 1 and Table 1 of Yuasa). Yuasa also provides (at Fig. 6) an alignment of full-length pre-S sequences from various DHBV isolates. Like Kyudyakov, Yuasa does not teach, or even suggest, a polypeptide that consists of a first amino acid sequence identical to 1 to 104 of a pre-S protein or a fragment thereof that includes amino acids 80-102, and one or more sequences not identical to any part of the pre-S protein. Further, Yuasa fails to teach or suggest the specific sequences recited in claims 2 to 5.

Finally, the Office Action cites Chassot, but applicants submit that Chassot does not provide the information missing from Khudyakov and Yuasa. Chassot describes experiments that identified five octapeptide antigenic domains within the DHBV pre-S region. The five domains are amino acids 7 to 14, 22 to 30, 58 to 65, 71 to 79 and 127 to 135 of the pre-S region (see Chassot at page 72, abstract). Other octapeptide antigenic domains (e.g., amino acids 82 to 95) are also mentioned. However, Chassot, like Yuasa, does not teach, or even suggest, the polypeptides recited in claims 1 to 5.

Based on the above, applicants respectfully submit that the Office Action has failed to establish a *prima facie* case for obviousness against claims 1 to 5. To establish *prima facie* obviousness, three basic requirements must be met: (1) there must be some motivation in the prior art to combine the cited references; (2) there must be a reasonable expectation of success; and (3) the prior art references must teach or suggest all of the limitations recited in the claims (see MPEP 2142). No *prima facie* case for obviousness has been established here because the Office Action fails to meet at least requirements (1) and (3).

First, the Office Action points to no evidence of a specific motivation to combine amino acids 1 to 104 (or portions thereof) of the pre-S sequences described in Yuasa and Chassot with sequences disclosed in Kudyakov. Instead, the Office Action points to two antigenic epitopes of the pre-S polypeptides described in these references and concludes (at pages 3 to 4):

> [I]t would have been obvious to those in the art to make a chimeric polypeptide as described in Khudyakov comprising these two epitopes. It is noted that the Chassot and Yuasa references teach other antigenic regions in addition to these. However, as these epitopes are disclosed as reactive with neutralizing antibodies, it would have been obvious to those in the art to use a polypeptide as described in Khudyakov comprising these epitopes to detect neutralizing DHBV antibodies in a sample. As the presently claimed polypeptides are obvious variants of the epitopic regions comprising these epitopes, the teachings of these references renders the claimed invention obvious. Those in the art would have had a reasonable expectation that the combination of these references to create the claimed polypeptide would result in a polypeptide effective for the identification of DHBV neutralizing antibodies.

To establish *prima facie* obviousness of a claimed invention, the prior art must provide a motivation and reasonable expectation of success to arrive at the specifically claimed polypeptides. The Office Action points to no evidence of a specific motivation to take, for example, amino acids 1 to 104 of the full-length pre-S polypeptide described in Yuasa (See Yuasa at Fig. 6) and combine it with sequences disclosed in Khudyakov. Such a motivation is nowhere to be found in the cited references.

At best, the Office Action describes a motivation to combine the specific epitopic sequences described in these references with sequences described in Khudyakov. Of course, even if a skilled artisan were to have done so, the artisan would not have arrived at applicants' claimed polypeptides. Nevertheless, the Office Action applies this motivation to applicants' specific polypeptides by characterizing them as "obvious variants" of sequences described in Chassot and Yuasa. Applicants submit that this is an improper and inaccurate characterization that causes the Office to leap to an erroneous finding of motivation and, ultimately, obviousness.

As applicants explained in their response to Office Action filed November 12, 2002, the presently claimed polypeptides were generated for specific purposes, e.g., to bind directly to

receptor p120 and/or p170 to interfere with hepadnavirus infectivity. None of the prior art references teaches or suggests that the prior art polypeptides have this activity. It is applicants' position that skilled practitioners would have had no motivation to make these specific polypeptides unless the practitioner appreciated their usefulness in p120 and/or p170 binding. Only after reading applicants' specification would the practitioner come to appreciate the usefulness of applicants' polypeptides. It appears that the Office used hindsight to conclude that applicants' polypeptides are "obvious variants" of the prior art sequences and that skilled practitioners would have been motivated by Khudyakov, Yuasa and Chassot to make them. This, of course, is impermissible.

Thus, applicants submit that the Office Action has failed to identify a proper motivation to combine the prior art references. Characterizing applicants' polypeptides as "obvious variants" of the prior art sequences is inaccurate and does not remedy this deficiency.

Second, the references cited in the Office Action clearly fail to teach all of the limitations recited in the claims. Neither Yuasa nor Chassot teaches the pre-S sequences specifically recited in these claims. Neither suggest these sequences. Applicants' claimed polypeptides would not be obtained no matter how the sequences described in Yuasa and Chassot are combined with those described in Kudyakov. Thus, applicants submit that the Office Action has failed to meet its burden on this score.

For the reasons stated above, applicants respectfully submit that the Office Action has failed to establish a prima *facie case* of obviousness against claims 1 to 5. Furthermore, even if a *prima facie* case of obviousness had been made (which it clearly has not), the claimed polypeptides have surprisingly advantageous properties. Applicants' specification describes two DHBV receptors (named "p170" and "p120" by applicants), and demonstrates that the two receptors specifically interact with discrete portions of the pre-S domain of the DHBV envelope protein. The specification demonstrates that synthetic pre-S polypeptides that block the binding sites on the p170 and p120 receptors interfere with DHBV infectivity (see the specification at page 42, lines 11 and 12). According to the specification, the presently claimed polypeptides are capable of binding to these receptors, interfering with DHBV infectivity. None of the references

cited by the Office Action states or even hints that the prior art polypeptides have this activity. Thus, the claimed polypeptides have the surprisingly advantageous ability to treat DHBV infection by a mechanism separate from an immune response raised against these polypeptides.

For the reasons discussed above, applicants respectfully request that this rejection be reconsidered and withdrawn.

Claims 6 to 9 were also rejected as allegedly obvious over Khudyakov in view of Chassot and Yuasa. As noted above, applicants have amended claim 6 to recite that the claimed polypeptide consists of, in addition to a first amino acid sequence, one or more amino acid sequences that are not identical to any part of a hepatitis B virus envelope protein. Applicants respectfully traverse this rejection with respect to amended claim 6 and dependent claims 7 to 9.

The content of Khudyakov was discussed above in relation to the rejection of claims 1 to 5. Applicants submit that Kyudyakov does not teach a polypeptide that consists of a first amino acid sequence identical to amino acids 25 to 161 of a pre-S protein, or a fragment thereof that includes at least amino acids 98 to 161, and one or more amino acid sequences that are not identical to any part of a hepatitis B virus envelope protein. Khudyakov does not suggest that such a polypeptide should be made. Additionally, Kyudyakov fails to teach or suggest the specific polypeptides recited in dependant claims 7 to 9, e.g., polypeptides wherein the first amino acid sequence is 87 to 161, 26 to 161, 59 to 161, 71 to 161, 80 to 161, 92 to 161 or 98 to 161 of SEQ ID NO:34, and polypeptides as recited in independent claim 6 that include the amino acid sequence of a glutathione S-transferase, as recited in claim 9.

The Office Action also cites Yuasa, which fails to provide the information missing in Khudyakov, the primary reference. The contents of Yuasa were also discussed above in relation to the rejection of claims 1 to 5. Yuasa does not teach, or even suggest, a polypeptide that consists of a first amino acid sequence identical to amino acids 25 to 161 of a pre-S protein, or a fragment thereof that includes at least amino acids 98 to 161, and one or more amino acid sequences that are not identical to any part of a hepatitis B virus envelope protein. Further, Yuasa , like Khudyakov, fails to teach or suggest the specific polypeptides recited in claims 7 to 9.

Finally, the Office Action cites Chassot, which does not provide the information missing from Khudyakov and Yuasa. The contents of Chassot were also discussed above in relation to the rejection of claims 1 to 5. Applicants submit that Chassot, like Yuasa, does not teach, or even suggest, the polypeptides recited in claims 6 to 9.

For the reasons discussed above and with respect to the rejection of claim 1 to 5, applicants submit that Khudyakov, Yuasa and Chassot provide no motivation to skilled practitioners to make applicants' polypeptides. Thus, applicants submit that the Office Action has failed to establish a *prima facie* case for obviousness against claims 6 to 9. Furthermore, even if a *prima facie* case of obviousness had been made (which it has not), the claimed polypeptides have surprisingly advantageous properties, as discussed above. For these reasons, applicants request that the present rejection be reconsidered and withdrawn.

CONCLUSION

Applicants submit that all claims are in condition for allowance, which action is requested. Enclosed is a check for $475 for the Petition for Extension of Time fee for a three month extension. Please apply any other charges or any credits to Deposit Account No. 06-1050, referencing Attorney Docket Number 00786-287004.

Respectfully submitted,

Date: 8/10/04

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